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Title: Agency performance modulates resting-state variation in prefrontal brain regions

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Abstract: Distinguishing the effects of own from others' actions is a prerequisite for effective interpersonal functioning. Individuals differ in their ability to do this. For example, difficulties in self-other differentiation have been linked to positive symptoms of schizophrenia such as hallucinations, with causally ambiguous situations proving a universal challenge. Indeed, difficulties in this area have been shown to characterise non-clinical samples who self-report higher levels of positive schizotypy. The goal of the present study was to examine relationships between individual differences in resting-state functional connectivity and self-other attribution performance. Fifty-five healthy adults completed a resting-state fMRI scan and a task that systematically modulated the probability that finger taps of self versus other would generate auditory tones. Using group independent component analysis (ICA) and dual regression, we found that connectivity between prefrontal networks and other brain regions increased as overall performance decreased and misattribution biased towards other increased. These findings shed additional light on the neural mechanisms of agency, emphasising that connectivity with prefrontal networks play an important role in self-other differentiation.

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Regarding: submission of research article manuscript titled: "Agency performance modulates resting-state variation in prefrontal brain regions"

To the editor:

RE; MS title and authors

I would be grateful if you would consider the above MS for publication in Neuropsychologia.

The study is an advance in the methods used to assess and understand self-other agency in relation to brain function. To our knowledge, this is the first attempt to examine spontaneous fluctuations in neural response during resting-state fMRI in relation to individual differences in the ability to differentiate self- from other-generated events. Our findings show that task performance modulates within- and between network connectivity in prefrontal networks, with increased connectivity associated with lower task performance. Using a parametric design manipulating probability of self-other control, we were also able to show connectivity patterns more specifically related to bias (towards self or other) in ambiguous conditions.

We consider this to be a step towards an increased understanding of how we process situations – such as complex social encounters – where information for distinguishing self- from other-produced intentions and actions is reduced. Given the well-established link between positive schizotypy and reduced agency performance, this research speaks to theoretical models relating to the origins of passivity phenomena typically seen in the context of psychosis.

This paper has been previously reviewed by NeuroImage (Ms. No.: NIMG-16-813), a member of the Neuroscience Peer Review Consortium (NPRC). Given that the issues highlighted by the two reviewers are unrelated and seem addressable, we have decided to submit an edited version of the manuscript, taking reviewers' comments into account. In accordance with NPRC procedures, following submission we will request that reviewers' comments are forwarded to you. However, comments have also been included below alongside our responses to make clear the rational behind changes make to the original submission.

Regards,
Christophe de Bézenac

UNIVERSITY OF LIVERPOOL

RESPOSE TO REVIEWERS

Ms. No.: NIMG-16-813
Title: Agency performance modulates resting-state variation in prefrontal brain regions
Corresponding Author: Dr. Christophe Emmanuel de Bézenac
Other authors: Dr Vanessa Sluming; Prof Rhiannon Corcoran

Preliminary notes:

- We would like to begin by thanking the reviewers for their thoughtful comments addressed below and their role in improving the submission.
- Reviewer comments are highlighted in grey while changes to the manuscript are shown in yellow

Reviewer #1:

This is an interesting paper on a topic that is gaining interest in the field.
The authors provide a clear rationale and a clear context in their introduction and discussion. The methods are state of the art.
I only have a few minor comments:

Introduction:
The introduction provides a coherent and more or less complete overview of the literature. I miss however work done in Utrecht on agency processing using task-related fMRI, by Renes et al.

This reference has now been added to the text:

[p. 3] However, most other implicated regions have been primarily associated with action-outcome discordance typical of externally generated stimuli, though some have also shown sensitivity to self-agency (Renes et al., 2015).

[p. 22] Renes, R. A., van Haren, N. E., Aarts, H., & Vink, M. (2015). An exploratory fMRI study into inferences of self-agency. *Social cognitive and affective neuroscience*, *10*(5), 708-712.

Method:
My main concern is that I have difficulties understanding the task. I had to go back to the de Bezenac paper, which did make things clearer but I do have a few questions.

For example, how is it determined that 15 ms is the inherent delay and as such can be used as 'self' (threshold 90).
Secondly, do the thresholds 0-9 refer to percentage of taps with a inherent delay of 15 ms?

15 ms is the latency set manually in pure data between inputting a sound and hearing it emerge from the soundcard. It is a necessary buffer in digital audio systems and not likely to be perceived. The 15 ms delay applied to all generated sound (not just self-produced tones). Thresholds from 0-90 refers to the how conditions 1 to 10 were generated: "…a random number between 0 and 90 was generated on every tap; each condition was associated with a threshold above which tones generated by self would be heard and below which tones generated by other would instead be heard" (be Bezenac et al., 2015)

Third, when starting the task you do not have 50 previous fingertaps to use, how do you overcome this? A bit more information should be incorporated in the current paper, maybe as supplementary material.

A 3-min practice session that always begun with condition 1 allowed participant tap intervals to be recorded and used in non-self taps. The following has been added to the text:

[p. 6] The task took approximately 15 minutes to complete and was preceded by a 3-min practice session allowing 50 participant tap intervals to be recorded and used in non-self taps following randomisation.

The authors follow previous manuscripts and did not correct for multiple component testing in the within-network connectivity analyses. However, to provide the readers with a measure of strength of the effects, adding a few sentences of which of the findings would survive a correction is necessary.

This information has been added to the text as follows:

[pp. 8-9] Though correction has not been applied in similar studies, as an indication of the strength of the effect, the peak voxel in the statistical image reached a corrected p-value of 0.18 when false discovery rate (FDR) correction for multiple (10) network comparisons was applied. Ambiguity-related misattribution was also associated with increased connectivity between IC10 and the cerebellum (left Crus II; peak voxel = MNI coordinate -30 -72 -40, FWE corrected: p = 0.018) and reduced right inferior frontal gyrus (IFG) (homologue of Broca's area in the right hemisphere) connectivity with IC8, a left lateralised fronto-parietal network (peak voxel = MNI coordinate 52 28 -4, FWE corrected: p = 0.03, FDR correction for multiple (10) network comparisons, p=0.16).

Reviewer #2:

The authors present here an interesting study investigating the link between interindividual variability in agency ascription in an ambiguous context and functional coupling of large-scale brain networks at rest. Their behavioural task, already published in a previous work, is original and appealing since, contrary to most agency tasks that measure agency as an all-or-nothing process, it is suited to capture the phenomenon in its complexity.

The main findings were that the overall performance and misattribution scores were associated with inter- and intra-network connectivity, concerning above all medial and lateral prefrontal regions, encompassing structures belonging to the DMN.
I have sincerely found the approach employed here interesting for mainly two reasons. First of all, while large interindividual variability in agency performances are often observed, there are few studies that directly investigate the source of this variability. Thus, the present work can obviously constitute an important step forward in filling this gap. Second, I completely endorse the idea of employing large-scale networks functional integration measures, since they can constitute a more accurate fingerprint of cognitive phenomena.
Nevertheless, my enthusiasm for the study has been seriously undermined by what I consider a critical concern for the interpretation of the results.

As also stated by the authors in the discussion session, p. 12: "…participants' attribution judgments were based upon the temporal discrepancy between their actions and auditory outcome", it seems to me that their task heavily taps on timing abilities. Thus, to make any firm conclusion about the specific association between agency performances and resting state connectivity, the authors should have included at least a timing task (e.g., temporal order discrimination) and show that the performance on this task was not associated with the modulation of connectivity in the same networks. Briefly, without a control task I think that the reported results cannot be ascribed specifically to agency processes.
My doubts are also strengthened by the fact that modulation of connectivity are reported in areas also known to be involved in different aspects of timing processing, such as the cerebellum, and lateral frontal and parietal structures. See for example:

* Coull, J. T., Davranche, K., Nazarian, B., & Vidal, F. (2013). Functional anatomy of timing differs for production versus prediction of time intervals. Neuropsychologia, 51(2), 309-319.
* Coull, J. T. (2004). fMRI studies of temporal attention: allocating attention within, or towards, time. Cognitive Brain Research, 21(2), 216-226.
* Coull, J. T., & Nobre, A. C. (2008). Dissociating explicit timing from temporal expectation with fMRI. Current opinion in neurobiology, 18(2), 137-144.

Timing is indeed likely to be a primary cue in distinguishing self- from other-generated stimuli alongside other related features such as variation in intensity, shape and form, with the sensitivity to these cues being intricately tied up with agency performance. This is reflected in previous findings that also associate agency processing with neural response in regions implicated in temporal processing. However, previously used agency tasks have manipulated delay (e.g., Sato & Yasuda, 2005) and spatial displacement (e.g., Farrer et al., 2004) to introduce discrepancy between self-generated actions and outcome without the inclusion of temporal or spatial discrimination tasks. While it is clear that establishing the relative contribution of spatial-temporal cues (and participants' abilities to pick these up) to self-other differentiation has the potential to shed additional light on agency processing, we feel that the reviewer's very relevant point could also be aimed at previous agency work and therefore should first be the topic of a separate more in-depth investigation. Given how

little is known about between-individual variation in agency performance and the lack of network-based accounts of agency, we feel that the contribution that this paper makes is valuable despite its inability to disentangle temporal from agency processing. In light of the reviewers point the following has been added to the discussion section:

[p. 15] Finally, that cerebellar, frontal and parietal structures known to be involved in temporal processing (Coull, Davranche, Nazarian, & Vidal, 2013) were implicated in agency performance suggests that timing is an important cue for self-other differentiation and that there may be significant overlap between temporal discrimination and agency performance. This is in line with findings associating reduced performance on both timing and agency tasks to increased psychopathology (Papageorgiou et al., 2013; Carroll et al., 2008; Spence et al., 1997; Frith, 2005). Disentangling, and assessing the overlap between inter-individual variation in temporal/spatial discrimination and agency performance in relation to neural response in future work could further our understanding of agency-processing.

[pp. 16, 17, 21]

Carroll, C. A., Boggs, J., O'Donnell, B. F., Shekhar, A., & Hetrick, W. P. (2008). Temporal processing dysfunction in schizophrenia. *Brain and cognition*, *67*(2), 150-161.

Coull, J. T., Davranche, K., Nazarian, B., & Vidal, F. (2013). Functional anatomy of timing differs for production versus prediction of time intervals. *Neuropsychologia*, *51*(2), 309-319.

Papageorgiou, C., Karanasiou, I. S., Kapsali, F., Stachtea, X., Kyprianou, M., Tsianaka, E. I., ... & Papadimitriou, G. N. (2013). Temporal processing dysfunction in schizophrenia as measured by time interval discrimination and tempo reproduction tasks. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *40*, 173-179.

Linked to the previous comment, I think that another possible source of confound could be the effect of age. Indeed, the range of age is quite large in the sample (19-50 years). The effect of age on resting state networks connectivity is well documented, for a recent review see:

* Ferreira, L. K., & Busatto, G. F. (2013). Resting-state functional connectivity in normal brain aging. Neuroscience & biobehavioral reviews, 37(3), 384-400.

Moreover, timing abilities, for example in judgement of temporal order, show a decline with age, see:

* da Silva, C. F., Morgero, K. C. S., Mota, A. M., Piemonte, M. E. P., & Baldo, M. V. C. (2015). Aging and Parkinson's disease as functional models of temporal order perception. Neuropsychologia, 78, 1-9.

Thus, it is possible that the correlation between networks connectivity and task performance is simply due to a spurious correlation due to the link between performance

and age to the one hand, and age and reduced connectivity to the other hand. I strongly suggest to report correlation between task performance and age, and to control for age in the analyses testing the link between performance and connectivity. While this last issue can be easily ruled out by running supplementary analyses, I think that the first issue, those concerning the absence of a control task, represents a more serious concern.

We initially included age as a covariate into the GLM models without change to the presented findings. This may be because only three participants were aged between 40 and 50. There was also no correlation between age and other behavioural measures. Age as a possible confound is now acknowledged in the text and its correlation with the two performance measures are included as follows:

[p.8] Given the possible effect of age on temporal discrimination implicated in agency and resting state networks connectivity (Ferreira & Busatto, 2013), we tested the relationship between age and our variables of interest (OP; AM). OP did not correlate with age ($r(53) = 0.04$, $p=0.73$) and neither did AM ($r(53)=0.06$, $p=0.64$).

Highlights

- Agency performance modulated resting-state activity
- A medial prefrontal network extended into other regions with lower agency abilities
- Between-network connectivity increased with bias and lower performance

Agency performance modulates resting-state variation in prefrontal brain regions

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Abstract

Distinguishing the effects of own from others' actions is a prerequisite for effective interpersonal functioning. Individuals differ in their ability to do this. For example, difficulties in self-other differentiation have been linked to positive symptoms of schizophrenia such as hallucinations, with causally ambiguous situations proving a universal challenge. Indeed, difficulties in this area have been shown to characterise non-clinical samples who self-report higher levels of positive schizotypy. The goal of the present study was to examine relationships between individual differences in resting-state functional connectivity and self-other attribution performance. Fifty-five healthy adults completed a resting-state fMRI scan and a task that systematically modulated the probability that finger taps of self versus other would generate auditory tones. Using group independent component analysis (ICA) and dual regression, we found that connectivity between prefrontal networks and other brain regions increased as overall performance decreased and misattribution biased towards other increased. These findings shed additional light on the neural mechanisms of agency, emphasising that connectivity with prefrontal networks play an important role in self-other differentiation.

Keywords
Agency; prefrontal cortex; ambiguity; resting-state fMRI; independent component analysis

Highlights

- Agency performance modulated resting-state activity
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1. Introduction

Our waking day is filled with encounters that involve coordinating our own thoughts and behaviours with those belonging to other individuals. A prerequisite for doing this is the ability to distinguish acts of the 'self' from those of 'others' by forming accurate predictions about action-outcomes (Wolpert et al. 1995; Frith, 2005; Wegner, 2003). Even in the absence of others, we think about, and attempt to work out who is responsible for events that have or will take place. The sense of agency, the feeling that 'I am in control of my thoughts, actions and their consequences' (Gallagher, 2000) is a complex and multifaceted phenomenon that can be influenced by sensorimotor processes as well as by individuals' mental and emotional states; their intentions, expectations and biases (Synofzik, Vosgerau & Newen, 2008; Dijksterhuis et al., 2008; Farrer et al., 2008; Sato, 2009; Synofzik, Thier, & Lindner, 2006; Wegner, 2003).

Evidence suggests that individuals differ in their ability to objectively distinguish between events caused by self from those caused by other individuals. Difficulties associated with this fundamental skill is thought to be a core cognitive feature of schizophrenia, reflected in positive symptoms like delusions of control and auditory verbal hallucinations (Waters et al., 2012; Ditman & Kuperberg, 2005; Frith, 2005; Jeannerod, 2009; Spence et al., 1997). Performance discrepancies have also been shown in non-clinical samples (Sugimori, Asai, & Tanno, 2011; de Bezenac et al., 2015). For example, de Bezenac et al. (2015) found that accuracy in assessing the proportion of self-other control over auditory events decreased with hallucination proneness and, as anticipated, increased with music-making experience. This pattern of results was accentuated by task difficulty, i.e., in conditions where tones were as likely to belong to self as to other. Agency performance is therefore also determined by how an individual's previous experiences and expectations and cognitive biases interact with external factors (Wegner, 2002; 2003), such as the amount of prior information available to facilitate this decision-making.

Previous neuroimaging studies into sense of agency have examined brain activity as participants performed attribution tasks in the scanner. For example, studies have compared response to unaltered visual feedback of action with feedback that has been distorted using delay (e.g., Leube et al. 2003) or spatial displacement (e.g., Farrer et al. 2003; David et al. 2007). These paradigms have implicated a number of disparate regions involved in sensorimotor control and multimodal integration (for reviews see Sperduti et al., 2011, David et al., 2008). Some regions, such as the insula, display particular sensitivity to clearly self-produced outcomes (e.g., Farrer et al., 2003). However, most other implicated regions have been primarily associated with action-outcome discordance typical of externally generated stimuli, though some have also shown sensitivity to self-agency (Renes et al., 2015). These include the inferior parietal lobe (Farrer et al., 2003; Chaminade & Decety, 2002), extrastriate body area (EBA) (David et al., 2007), medial and dorsolateral prefrontal cortex (Pfeifer, Lieberman, & Dapretto, 2007; Schnell et al., 2007), and cerebellum (Blakemore et al., 1999; 2002).

Patients experiencing the positive symptoms of schizophrenia have shown over-

activation of the inferior parietal lobe (primarily associated with external causes) when performing attribution tasks (Spence et al., 1997; Jardri et al., 2011; Farrer et al., 2004). However, it is not yet clear how neural differences between individuals directly relate to agency performance. Increasing evidence suggests that inter-individual variation seen in the broad patterns of activation is meaningfully associated with cognitive and behavioural factors that constrain real world function (Bassett et al., 2009, van den Heuvel et al., 2009).

FMRI studies have examined individual differences in neural response, not only during experimental tasks, but also during so called 'resting-state' – in the absence of an explicit task. Resting-state networks (RSN) have been shown largely to correspond to regions that are co-activated during the performance of specific tasks and can provide complementary information about brain function, avoiding confounds related to completing a task (Smith et al., 2009). Emerging findings suggest that the temporal and spatial organisation of such networks have behavioural and clinical relevance (for reviews see Greicius, 2008; Zhang and Raichle, 2010) and remain relatively stable across time within individuals (Shehzad et al., 2009; Guo et al., 2012). RSN patterns in neurologically typical individuals have been associated with a number of cognitive function abilities relevant to agency, including working memory (Gordon et al., 2014; Hampson et al., 2006), attentional control (Kelly et al., 2008), and fluid reasoning (Cole et al., 2012) and theory of mind (Buckner & Carroll, 2007).

Network-based methods exploring co-activating areas have also been effective in highlighting neural differences between people with schizophrenia and matched controls (reviewed in Williamson and Allman, 2012; Karbasforoushan & Woodward, 2012). For example, severity of hallucinations and delusions were shown to correlate with aberrant functional connectivity in the default-mode network (DMN) (Rotarska-Jagiela et al., 2010), a set of brain regions associated in self-referential processing (Greicius et al., 2003; Christoff et al., 2011) and aspects of social cognition (Mars et al., 2012) including source attribution (reviewed in Northoff et al., 2006). The relationship between networks has also been shown to be clinically significant. For example, the anti-correlation typically observed between the DMN (the medial prefrontal area in particular) and the central executive network (CEN) (Wiebking et al., 2014), has been implicated in processes of self-other discrimination and shown to be attenuated in individuals at risk for psychosis (Spaniel et al., 2015; Wotruba et al., 2013). It has been argued that such neural differences may explain observed misattributions of internally or externally generated stimuli and that resting-state variation may play an important role in determining the sense of agency (Robinson, Wagner & Northoff, 2015).

Despite a shift towards considering networks as opposed to isolated regions as the unit of analysis in elucidating neural processes (Friston, 2011; Meehan & Bressler, 2012), network accounts of agency are scarce (David et al., 2007; David, Newen & Vogeley, 2008; Robinson, Wagner & Northoff, 2015). This line of research, however, has the potential to shed additional light on the functional relationships between brain regions previously implicated in self-other differentiation and the processes leading to agency difficulties and symptoms thought to be related to this facility. The current study aims to shed additional light on self-other processing by examining the relationship between performance on an agency task and functional connectivity in resting state fMRI. More specifically, we assessed the ability of 55 participants to

identify the proportion of auditory tones resulting from finger taps belonging to self as opposed to 'other' (composed of randomised taps of self; see de Bezenac et al., 2015), as well as the extent to which misattribution towards other increased in the most challenging ambiguous conditions. These measures were used to predict functional differences both within- and between-networks using a data-driven approach involving group independent component analysis (ICA) and dual regression (Beckmann & Smith, 2005; Beckmann et al., 2009; Filippini et al., 2009).

Given the limited scope of prior research on functional connectivity and agency, the current study had a number of objectives: to (1) determine whether patterns of functional connectivity are associated with individual differences in overall task performance and in ambiguity-related misattribution; (2) examine whether such differences are associated with RSNs composed of regions previously implicated in agency tasks; and (3) investigate how individual differences in agency performance might predict alterations in either the connectivity of RSNs with other brain regions or other large-scale RSNs. Our hypothesis was that between-individual variation in functional connectivity during rest would be associated with agency performance measures and, more specifically, in the light of previous clinical evidence, that DMN nodes would be implicated. However, based on the lack of prior research in this area, our investigation was more exploratory with regard to how exactly such individual differences would be expressed.

2. Methods

2.1. Participants

The study sample initially consisted of 57 right-handed participants with a mean age of 25 years (SD = 8; range, 19–50). Participants were recruited from the student and staff population at the University of Liverpool. All participants reported normal or corrected-to-normal vision, normal hearing and somatosensory perception. No participants reported histories of mental or neurological illness. Two participants were excluded prior to statistical analysis due to incidental neurological abnormalities, leaving a final sample of 55 participants (28 females). All participants gave written informed consent as part of a protocol approved by the ethics committee of the University of Liverpool.

2.2. Imaging protocol

Participants completed a resting-state scan: they were asked to relax with their eyes closed for a duration of six minutes. Scans were obtained using a Trio 3.0 Tesla (Siemens, Erlangen, Germany), whole body MRI system, equipped with an eight-channel phased array head coil. Foam padding and head restraints were used to minimise head movement during imaging. Each scan consisted of 197 contiguous EPI functional volumes (TR = 2000 ms; TE = 25 ms; flip angle = 90°, 32 slices, matrix = 64 x 64; FOV = 192 mm; acquisition voxel size = 3.5 mm3). Before preprocessing these functional data, the first eight volumes of each run were automatically removed to allow for magnetic stabilization, leaving 180 usable volumes. To facilitate co-registration and normalization of these functional data, we also acquired a high-resolution T1-weighted magnetization prepared gradient echo sequence from each participant that lasted 12 minutes (TE 5.57ms, TR 2040 ms, flip angle 8º, FOV=256×256 mm2, 176 slices, voxel size 1×1×1 mm3).

2.3. Behavioural task

Following the scanning session, participants completed a computerised agency task previously described in de Bezenac et al., (2015). Briefly, participants were asked to perform series of irregular taps ("like Morse code") using their right index finger whilst listening to a sequence of tones on headphones. Tones either resulted from the participant's actions (self) or from the actions of 'other', which consisted of the previous 50 inter-tap intervals performed by the participant played back in a random order. The probability that self- or 'other'-generated taps would produce tones was manipulated in 10 equal steps corresponding to 10 conditions, allowing a continuum ranging from tone control belonging fully to self (C1) to control belong fully to other (C10). In the middle of the continuum (C5, C6), the probability of self- and other-generated tones was equal, making self-other attribution more ambiguous. After a 3-minute practice session, each participant completed a total of 50 trials made up of 5 repetitions of each of the 10 conditions presented in a pseudorandom order (consecutive conditions were not presented consecutively). After each trial, consisting of 10 seconds of tapping, participants were asked to assess the proportion of control that they felt belonged to self versus to other along a continuum, using a computer mouse. The task took approximately 15 minutes to complete and was preceded by a 3-min practice session allowing 50 participant tap intervals to be recorded and used in non-self taps following randomisation. A schematic representation of the experimental paradigm is provided in Fig. 1 (left).

2.4. Behavioural variables

Overall performance (OP) was calculated as the correlation between participants' attribution ratings (subjective locus of control) ranging from self to other and tap-tone asynchrony (objective locus of control). The latter was computed as the correlation between Butterworth filtered time-series of tap and tone onsets. A high correlation thus indicated that the subjective locus of control experienced by the participant matched the actual or objective locus of control instantiated in the task.

Misattribution (attribution error) was calculated as the difference between attribution rating (ranged between 0 and 1) and tap-tone asynchrony (also ranged between 0 and 1). Given that misattribution has been shown to peak in the middle of the self-to-other continuum (C5-C6) (de Bezenac et al., 2015), we represented ambiguity-related misattribution (AM) as the slope (b_1) of a regression line predicting misattribution by pooling conditions 1 and 10, 2 and 9, 3 and 8, 4 and 7, and 5 and 6. Positive values represent misattribution biased towards 'other' in ambiguous conditions (the middle as opposed to the extremes of the self-to-other continuum) with negative values indicating ambiguity-related misattribution biased towards self.

2.5. Image preprocessing

FMRI data processing was carried out using FEAT (FMRI Expert Analysis Tool) Version 6.00, part of FSL (FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl). Preprocessing steps included motion correction (Jenkinson et al., 2002), non-brain removal (Smith, 2002), spatial smoothing (FWHM 5mm), grand-mean intensity normalisation, highpass temporal filtering (Gaussian-weighted least-squares straight line fitting, with sigma=55.0s). Registration to high-resolution structural and Montreal Neurological Institute (MNI) 152 stereotactic space (2 mm) images was carried out using default settings in FLIRT and a linear transformation with 12 degrees of

freedom (Jenkinson & Smith, 2001, Jenkinson et al., 2002).

2.5. Within-network connectivity: dual regression ICA

The overall group preprocessed data consisting of 55 participants were temporally concatenated and entered into an ICA using MELODIC (Version 3.13) (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/MELODIC) in FSL. Data were decomposed into 20 spatially and temporally distinct components in order to represent robust large-scale networks (Beckmann et al. 2005; Greicius et al. 2007; Smith et al., 2009). Visual inspection (Kelly et al., 2010) of these group-level ICs was used to identify those best representing previously identified networks (Laird et al., 2011; Smith et al., 2009), while components that did not match these networks were considered noise or artifacts such as movement, white matter, or ventricles. Spatial cross-correlation were also conducted to confirm IC-network associations.

Non-artifactual ICs were then compared to participant-specific timecourses and spatial maps using dual regression (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/DualRegression). This involved: (1) regressing the group-spatial-maps into each participant's functional dataset to give a set of time-series; (2) regressing these time-series into the same dataset to get a participant-specific set of spatial maps; and (3) comparing the spatial maps across participants to look for positive and negative differences predicted by the behavioural variables (after accounting for mean group connectivity). Non-parametric permutation testing was carried out as part of the latter (step 3) using the randomise tool in FSL (5000 permutations) and resulting statistical maps were thresholded using threshold-free cluster enhancement with an alpha level of .05 (corrected). Following studies using similar procedures (Uddin, Supekar, & Menon, 2013; Nomi & Uddin, 2015), correction for multiple component testing was not applied.

2.6. Between-network connectivity: FSL Nets

Between-network differences in functional connectivity were examined using the FSL Nets package implemented in Matlab (http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FSLNets). This analysis involved correlating participant-specific time-series from the dual regression (step 1) for each IC pair (Smith et al., 2010). Behavioural variables were then used to predict full and partial correlation values using randomise (5000 permutations).

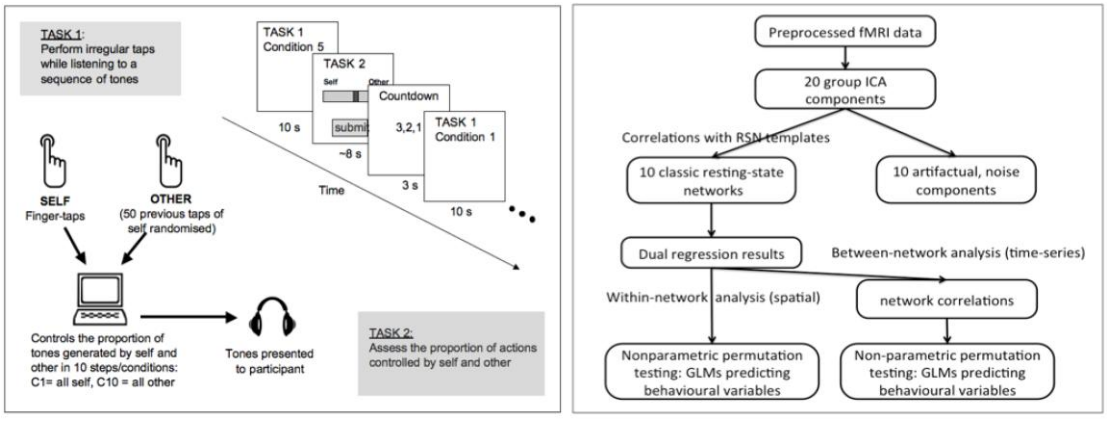

Fig. 1. Behavioural task depiction (left) and processing pipeline for resting-state fMRI data (right).

3. Results

3.1. Behavioural data

The data was found to be suitable for the proposed analyses, without floor or ceiling effects and with scores varying sufficiently across the group of participants. The 55 participants had a mean OP (*r*) score of 0.77 (SD = 0.1, range = 0.51 to 0.94) and a mean AM (b_1) score of 0.33 (SD = 0.2, range= -0.08 to 0.73). Confirming previous results (de Bezenac et al., 2015), the positive AB score in all but one participant indicates a general bias towards other in the middle of the self-to-other continuum. Given the possible effect of age on temporal discrimination implicated in agency and resting state networks connectivity (Ferreira & Busatto, 2013), we tested the relationship between age and our variables of interest (OP; AM). OP did not correlate with age ($r(53) = 0.04$, $p=0.73$) and neither did AM ($r(53)=0.06$, $p=0.64$).

3.2. Group ICA

Of the 20 ICs extracted from the group of 55 participants, 10 were determined to be artifactual, representing cerebral spinal fluid, ventricles, head motion, signal drop-out and white matter response. The 10 remaining ICs seen on Fig. 2 were entered into the dual regression analysis and corresponded to default mode (IC1, $r = .75$; IC4, $r = .36$), right frontoparietal (IC2, $r = .59$), visual (IC3, $r = .66$), sensorimotor (IC5, $r = .59$), auditory (IC6, $r = .6$), dorsal attention (IC7, $r = .45$), left frontoparietal (IC8, $r = .65$), executive control (IC9, $r = .67$), and frontal (IC10, $r = .52$) networks.

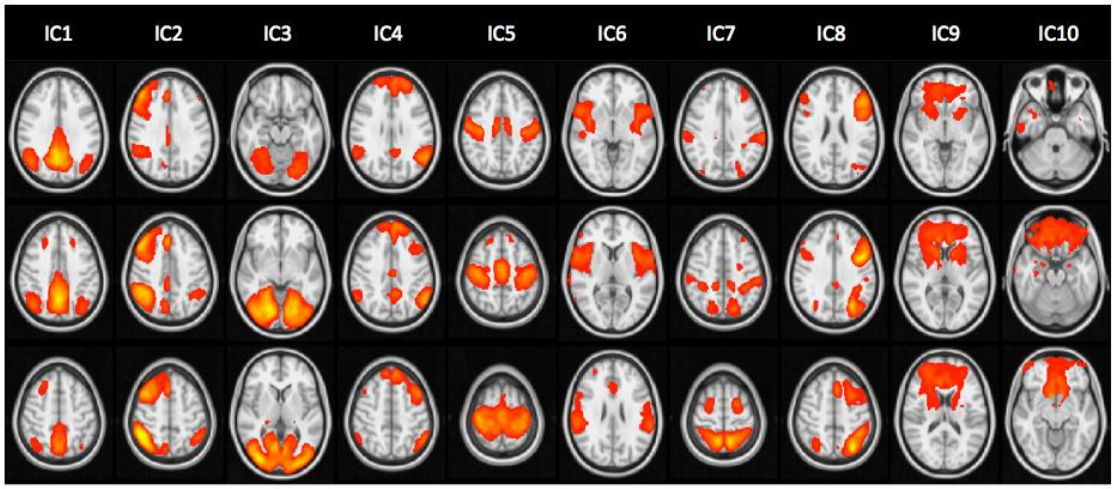

Fig. 2. Independent components (IC1-10) included in the analysis. Statistical images are shown in radiological convention with the right hemisphere displayed in the left.

3.3. Within-network connectivity

As seen in Fig. 3 and Table 1, lower OP (the correlation between subjective and objective action attribution) was associated with increased connectivity of IC10, a medial frontal network spatially (IC10, $r = .29$) and temporally (see Fig. 4) linked to the DMN, with a number of brain regions, including the paracingulate and anterior cingulate regions (peak voxel = MNI coordinate 4 44 -6, FWE corrected: p = 0.026), lateral occipital gyrus (peak voxel = MNI coordinate 50 -64 -2, FWE corrected: p = 0.028), and cerebellum (right VI). Though correction has not been applied in similar studies, as an indication of the strength of the effect, the peak voxel in the statistical

image reached a corrected p-value of 0.18 when false discovery rate (FDR) correction for multiple (10) network comparisons was applied. Ambiguity-related misattribution was also associated with increased connectivity between IC10 and the cerebellum (left Crus II; peak voxel = MNI coordinate -30 -72 -40, FWE corrected: p = 0.018) and reduced right inferior frontal gyrus (IFG) (homologue of Broca's area in the right hemisphere) connectivity with IC8, a left lateralised fronto-parietal network (peak voxel = MNI coordinate 52 28 -4, FWE corrected: p = 0.03, FDR correction for multiple (10) network comparisons, p=0.16).

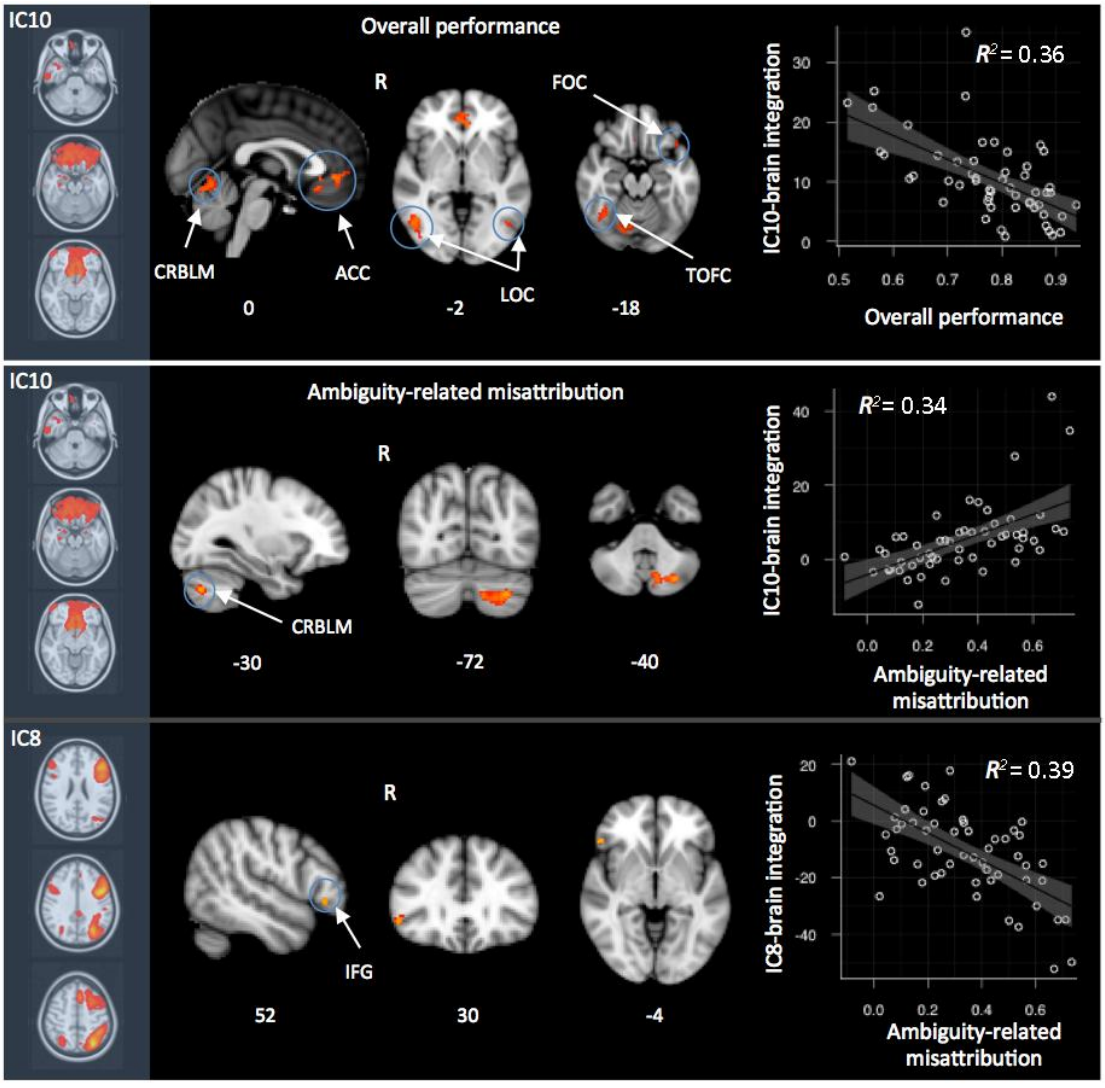

Fig. 3. Within-network connectivity. Task performance predicting brain regions with functional connectivity to IC10 (medial frontal network) (top panel); Ambiguity error predicting brain regions with functional connectivity to IC10 (medial frontal network) (middle panel) and IC8 (left fronto-parietal network). Corrected for multiple comparisons (grey matter voxels) using threshold-free cluster enhancement, shown at P < 0.05, corrected. The right side of images represents the left side of the brain. Scatterplots show the relationship between the behavioural variable (x-axis) and the degree of integration between the network and all significant voxels in the statistical image (y-axis).

Network	Structures to which each cluster belongs to	Side	BA	N	P-value	MNI coordinates		
						X	y	z
IC10: reduced overall performance								
	Lateral Occipital Cortex, inferior division (12), Occipital Fusiform Gyrus (10)	R	37	705	0.028	50	-64	-2

Paracingulate Gyrus (28), Cingulate Gyrus, anterior division (23), Subcallosal Cortex (24)	R	10	252	0.026	4	44	-6
Lateral Occipital Cortex, inferior division (25), Inferior Temporal Gyrus, temporooccipital part (15)	L	37	89	0.036	-46	-60	0
Right Crus II (69), Right Crus I (19)	R	n/a	47	0.036	24	-86	-36
Lingual Gyrus (34)	R	18	10	0.043	14	-84	-12
Frontal Orbital Cortex (55)	L	38	9	0.044	-42	22	-18
Right VI (89)	R	n/a	8	0.048	28	-58	-30
Right VI (81), Right V (19)	R	n/a	4	0.049	16	-60	-22
Frontal Orbital Cortex (68)	L	38	3	0.048	-36	22	-8
Temporal Occipital Fusiform Cortex (34)	L	19	3	0.047	-20	-58	-14
IC10: increased ambiguity-related misattribution							
Left Crus II (44), Left VIIb (21)	L	n/a	257	0.018	-30	-72	-40
Left Crus I (52), Left Crus II (33)	L	n/a	27	0.04	-10	-78	-32
IC8: reduced ambiguity-related misatribution							
Inferior Frontal Gyrus (40), pars triangularis, Frontal Orbital Cortex (17)	R	38	11	0.032	52	28	-4

Table 1. Within-network dual regression results. MNI coordinates for peak voxels are provided for each cluster with associated p-values corrected using threshold-free cluster enhancement. Values after each brain regions represents the associated cluster percentage. N = number of voxels; IC = independent component; BA = Brodmann area.

3.4. Between-network connectivity

Fig. 4 shows the correlation values of IC pairs. Squares below the diagonal line represent full correlation network comparisons, which allow for the influence of other ICs, while the partial correlations displayed above the diagonal line represent more direct measures of the relationship between IC pairs.

Using performance as predictor, the between-network comparison showed one significant difference for partial correlation values between IC9, corresponding to a frontal executive control network, and IC3, a visual network (Fig. 4, labeled OP; FWE corrected: $p = .019$). Higher OP during the agency task predicted significantly smaller correlation values between these two networks. No other differences emerged for full or partial correlation with performance as the predictor (FWE corrected: $p > .14$). Increased misattribution towards other in ambiguous conditions in the middle of the self-to-other continuum predicted increased full correlation between IC9 (the same frontal executive control network) and IC7, a dorsal attention network (Fig. 4, labeled AM, FWE corrected: $p = .035$). No other differences emerged for between-network comparisons (FWE corrected: $p > .9$).

IC9 implicated in both performance measures included subcortical regions and spatially correlated with the salience network ($r = 0.3$). Across participants, partial correlation comparisons showed that response fluctuation in this frontal network (IC9) correlated with IC6 (a temporal network) ($r = 0.84$) and IC4 (a DMN) ($r = 0.63$) and was negatively related to IC8 (a left-lateralised frontoparietal network) ($r = -0.42$). IC7, a dorsal attention network, was anti-correlated with IC4 (a DMN) ($r = -0.79$) and correlated with IC2 (a right-lateralised frontoparietal network) ($r = 0.9$) (see Fig. 4).

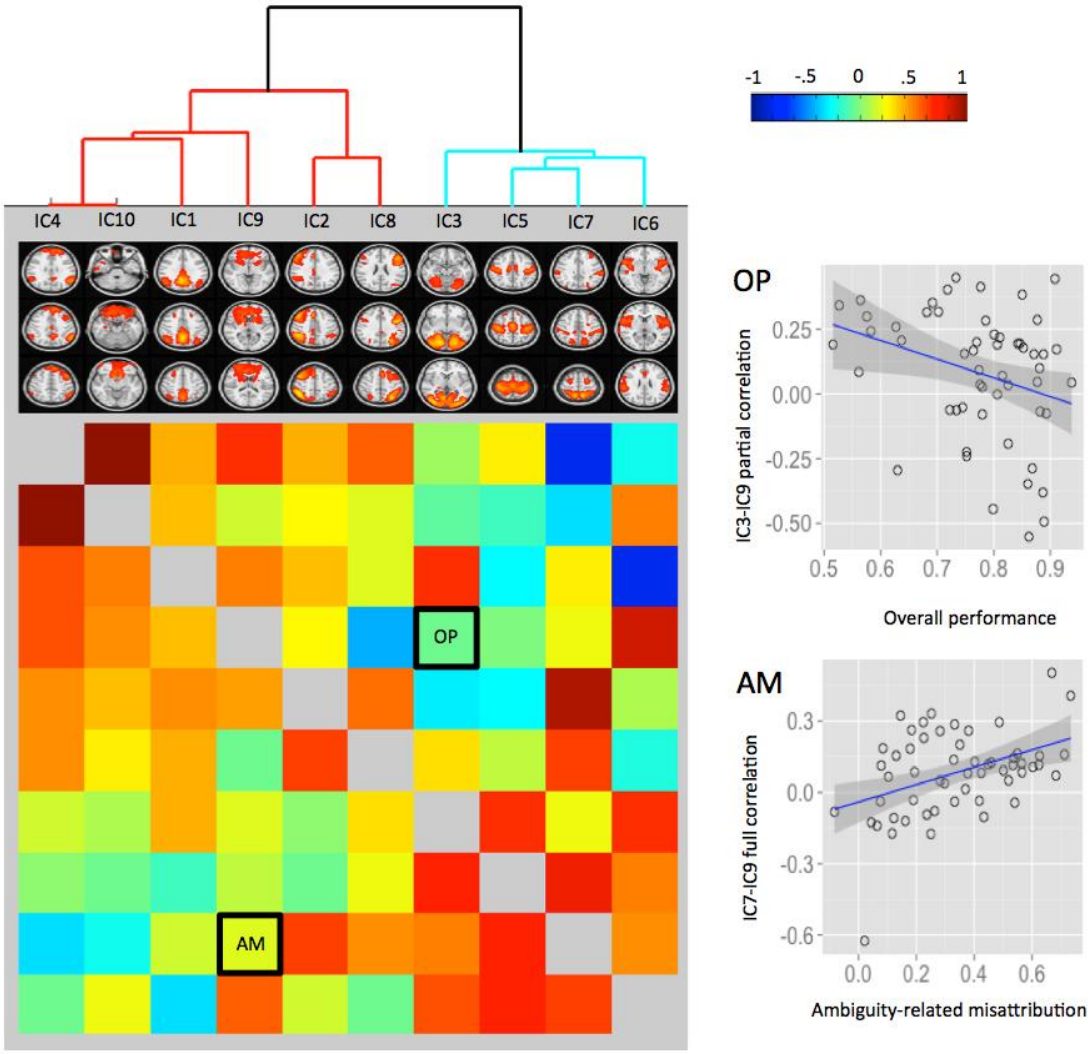

Fig. 4. Between-network connectivity (IC1-10). The right side of the images represents the left side of the brain. Full correlations across the cohort are shown below the diagonal line of the correlation matrix (left) with partial correlations shown above it. IC groupings on top of the matrix represent hierarchical clustering of IC timeseries. OP (overall performance) represents a significant decrease in partial correlations between IC3 (visual network) and IC9 (executive control network) (FWE corrected: $p = .019$). AM (ambiguity-related misattribution) represents a significant increase in full correlations between IC7 (visual/attention network) and IC9 (executive control network) (FWE corrected: $p = .035$). Corresponding scatterplots are shown on the right.

4. Discussion

Using resting state fMRI and an agency task, we investigated whether functional connectivity within and between networks during rest varies in relation to individual differences in agency task performance. Our findings indicate that lower overall performance and increased ambiguity-related misattribution was associated with increased connectivity between a medial prefrontal network (the anterior DMN) and other brain regions, including the anterior and paracingulate cortex, lateral-occipital gyrus, and the cerebellum. Ambiguity-related misattribution predicted reduced connectivity of a left lateralised frontoparietal network with the inferior frontal gyrus (Broca's area homologue in the right hemisphere). Connectivity (correlation) between a second more lateral prefrontal network and a visual and attention-related network

was also related to lower performance.

4.1. Within-network functional connectivity and overall performance

The association between agency performance in our task and variation in a medial prefrontal network is consistent with studies that implicate this region in agency through its putative role in performance monitoring (reviewed in Van Noordt & Segalowitz, 2012). The medial prefrontal cortex (MPFC) has specifically been implicated in organising behaviour in the temporal domain (Fuster, 1997, 2001; reviewed in Vogeley & Kupke, 2007). This temporal association makes sense in the context of the task used here because participants' attribution judgments were based upon the temporal discrepancy between their actions and auditory outcome. Imaging studies also suggest that the MPFC is a key substrate for social cognition (Gallagher et al., 2000; Goel, 1995), integrating self-other information across time (reviewed in Van Overwalle, 2009). With reciprocal connections to brain areas associated with memory (hippocampus), emotion processing (amygdala) and higher-order information processing (DLPFC), this region is thought to be play a regulatory role goal-directed behaviour (reviewed in Wood, & Grafman, 2003).

As an anterior node of the DMN (Buckner, Andrews-Hanna & Schacter, 2008), the MPFC is thought to play an important role in maintaining the sense of self, showing particular sensitivity to self-referential processing, while posterior nodes (i.e., PCC; IPL) respond to stimuli relating to others (Northoff and Bermpohl, 2004; Molnar-Szakacs & Uddin, 2013). For example, the MPFC has previously been associated with the retrieval of autobiographical memory (Svoboda et al., 2006), remembering self- versus externally-generated words (Vinogradov et al., 2008), self-referential episodes (Zysset et al., 2002) and self-knowledge (reviewed in Van Overwalle, 2009). It may be that agency performance is more determined by how regions associated with self are related to the rest of the brain than by regions associated with processing of other.

The DMN and its anterior node in particular has also received considerable interest in the study of neuropsychiatric conditions associated with agency dysfunction. For example, combined structural and functional imaging conducted by Pomarol-Clotet et al. (2010) revealed overlapping regions of abnormality in the MPFC in people with chronic schizophrenia compared to matched controls. Similarly, reduced task-related deactivation of the MPFC (Whitfield-Gabrieli et al., 2009; Pomarol-Clotet et al., 2008) and over-activation of this region during rest (Unschuld et al., 2014) has been associated with cognitive deficits related to schizophrenia. This pattern of findings is consistent with the direction of our results given the established link between positive schizotypy and reduced agency performance (Frith, 2005; Jeannerod, 2009).

In particular, this network expanded into neighbouring anterior cingulate regions previously associated with agency-relevant functions such as conflict monitoring, attention, decision-making, and emotional regulation (reviewed in Devinsky, Morrell & Vogt, 1995; Paus et al., 1998; Botvinick, Cohen & Carter, 2004). One model of the ACC proposes that it interacts with other prefrontal regions, combining executive processes with representations of emotional states to enable appropriate behavioural responses to events relevant to self (Paus, 2001). Interestingly, anterior cingulate regions are also amongst those that have been consistently implicated in hallucination-related phenomena (reviewed in Allen et al., 2008; Fornito et al., 2009). Notable examples include relationships found between psychosis proneness and over-

activation in the ACC during self-reflection (Modinos et al., 2011), and between the morphology of the paracingulate sulcus and hallucinatory experiences (Garrison et al., 2015).

In our findings prefrontal connectivity with a lateral occipital, inferior temporal region and the cerebellum also increased in association with lower overall performance. The former includes the "extrastriate body area" (EBA) – a region often implicated in agency tasks with particular sensitivity to externally-generated stimuli (David et al., 2007; 2008; reviewed in Jeannerod, 2004), in addition to its association with embodiment (Arzy et al., 2005). This region is also just posterior to the inferior parietal lobe also shown to be sensitive to action-outcome discrepancy that characterises externally-caused events and found to be overactive during agency tasks in patients with positive symptoms of schizophrenia (e.g., Farrer et al., 2004; Spence et al., 1997).

Similarly, regions of the cerebellum have been associated with other-agency and action feedback discrepancy (Blakemore et al., 2001). Though still little is known about the fronto-cerebellar pathway, it has been suggested that it may facilitate functions that are implicated in agency processing such as the transfer of sensorimotor information and motor prediction and learning (Watson et al., 2015; Kalmbach et al., 2009). Compared with healthy controls, first-episode schizophrenia patients show increased resting state connectivity between DMN and the cerebellum (right Crus II) (Guo et al., 2015).

More generally, it makes sense that connectivity between regions associated with self (MPFC) and those associated with other increased with lower performance. This suggests that self-other differentiation depends on regions associated with self and other being functionally distinct from one another. This rational is in line with findings of overlap between the self and non-self cortical maps in individual with positive symptoms of schizophrenia (Jardri et al., 2011).

4.2. Within-network functional connectivity and ambiguity-related misattribution

Confirming previous behavioural findings (de Bezenac et al., 2015), ambiguity-related misattribution was biased towards other, suggesting a tendency to experience self-generated events as belonging to other in ambiguous situations where the likelihood of self and other-generated tones was equal. The extent of this bias also implicated the medial frontal network, specifically predicting increased connectivity with the cerebellum (Left Crus II). More specific examination of functional fronto-cerebellar pathways may therefore contribute to a clearer understanding of the role that the cerebellum plays in agency and in social cognition more generally (Van Overwalle et al., 2014).

The only regions that showed increased network connectivity in relation to better performance and, more specifically, reduced ambiguity-related misattribution towards other was an area in the IFG that corresponded to the right homologue to Broca's area. Activity in this region has been shown to be responsive to self-specific stimuli (Uddin et al., 2005; Kaplan et al., 2008; Qin & Northoff, 2011) and has been implicated in the experience of auditory verbal hallucinations (Sommer et al., 2008). In our findings, reduced ambiguity-related bias was associated with increased connectivity between this region and the left lateralised frontoparietal network that

includes Broca's area. Using dynamic causal modelling, Ćurčić-Blake et al. (2013) found reduction in connectivity between Broca's area and its right homologue in patients with hallucinations. Furthermore, reduced connectivity between the latter and the left temporoparietal junction (TPJ), part of the left frontoparietal network has also been associated with hallucinations (Vercammen et al., 2010). It may be that cross-hemisphere co-activation of these regions reduces the likelihood of experiencing self-generated action and thoughts as originating from an external source. This could be tested experimentally in by using neuro-stimulation techniques to modulate functional relationships between aforementioned regions during an agency task or with patients experiencing hallucinations (Moseley, Fernyhough, & Ellison, 2013).

4.3. Between-network functional connectivity

Examining connectivity between networks, both agency performance measures were associated with the more lateral, executive control prefrontal network (Smith et al., 2009; for reviews see Botvinick et al. 2004; Dosenbach et al. 2007). This network spatially overlapped with the salience network and included subcortical regions and response fluctuations correlated with a temporal and default mode network. That agency performance modulated a frontal network commonly engaged by tasks requiring executive control is not surprising given the high-level functions likely to be involved in self-other processing. Such prefrontal regions are thought to regulate the flow of ongoing processing via dopaminergic neurotransmitters, particularly affecting systems responsible for perception, action selection, and emotional evaluation (Miller & Cohen, 2001).

Our findings show that correlation between this frontal network and a visual network increased as overall agency performance decreased. While it is not immediately apparent why a visual network was implicated in agency performance, it suggests that autonomy between prefrontal and perceptual brain areas during resting state has important implications for accurate agentic decision-making.

Ambiguity-related misattribution increased with correlation between the same frontal network and a dorsal attention network with fluctuations highly correlated with a right-lateralised frontoparietal network and anticorrelated with a DMN across participants. While further hypothesis-driven research is required, our pattern of results suggests that individuals who have a tendency to experience their actions as belonging to others in the absence of clear information for self-other differentiation may be hyper-attentive/vigilant during rest, a trait previously observed in people with schizophrenia (Mar, Smith & Sarter 1996). Given the previous link between ambiguity processing and hallucination proneness (de Bezenac et al., 2015), this finding indirectly supports evidence implicating the deregulation of task-positive and task-negative networks in schizophrenia (Wotruba et al., 2013; Nygård et al., 2012). However, ambiguity-related misattribution was only a significant predictor in the full-correlation comparison, suggesting that the effect may be modulated by another network. Hypotheses-driven mediation models could be used in future work to uncover indirect relationships.

4.4. General

With the exception of the finding relating agency performance to left frontoparietal connectivity with the right IFG, connectivity within and between networks was related to lower performance (including increased ambiguity-related misattribution).

This is in line with studies that associate neural inhibition, particularly of the DMN, to task difficulty and performance accuracy (Harrison et al., 2011; Gilbert et al., 2012; Polli et al., 2005; Engström, Landtblom, & Karlsson, 2013), as well as those showing general over-activation and connectivity to be associated with schizophrenia (Whitfield-Gabrieli et al., 2009; Peeters et al., 2015; Shim et al, 2010; Yang et al., 2014). For example, Driesen et al. (2013) found that schizophrenia-like symptoms induced through ketamine were associated with increased global functional connectivity between networks that are normally functionally independent during resting-state fMRI. This hyperconnectivity seems to specifically implicate prefrontal areas (Vollenweider et al., 1997; Whitfield-Gabrieli et al., 2009; Anticevic et al., 2015). Our findings, showing that two prefrontal networks were modulated by agency performance suggests a specific role for the prefrontal cortex and its functional connections with other parts of the brain in self-other processing. An over-connected prefrontal lobe could mediate distorted boundaries between self and others and lead to lower attribution performance. Given the correlation between fluctuation in the medial frontal network and the DMN, our findings partially support theoretically-driven predictions implicating the DMN in self-other differentiation (Robinson, Wagner & Northoff, 2015).

Finally, that cerebellar, frontal and parietal structures known to be involved in temporal processing (Coull, Davranche, Nazarian, & Vidal, 2013) were implicated in agency performance suggests that timing is an important cue for self-other differentiation and that there may be significant overlap between temporal discrimination and agency performance. This is in line with findings associating reduced performance on both timing and agency tasks to increased psychopathology (Papageorgiou et al., 2013; Carroll et al., 2008; Spence et al., 1997; Frith, 2005). Disentangling, and assessing the overlap between inter-individual variation in temporal/spatial discrimination and agency performance in relation to neural response in future work could further our understanding of agency-processing.

5. Conclusion

Using a data-driven approach, we present initial evidence for the relevance of the anterior brain's resting state activity in agency processing. Increased connectivity of the prefrontal cortex with other parts of the brain related to a diminished ability to distinguish self from other-generated events. More specifically, lower performance predicted increased connectivity between medial prefrontal regions associated with self-referential processing and regions shown to be sensitive to externally-generated stimuli. On the basis of these findings we contend that a greater understanding of agency-related patterns of functional connectivity during rest has potential to contribute to theories of self-other representation in the brain and, importantly, to enhance our understanding of conditions, like psychosis, where such representations are challenged.

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Figure 1

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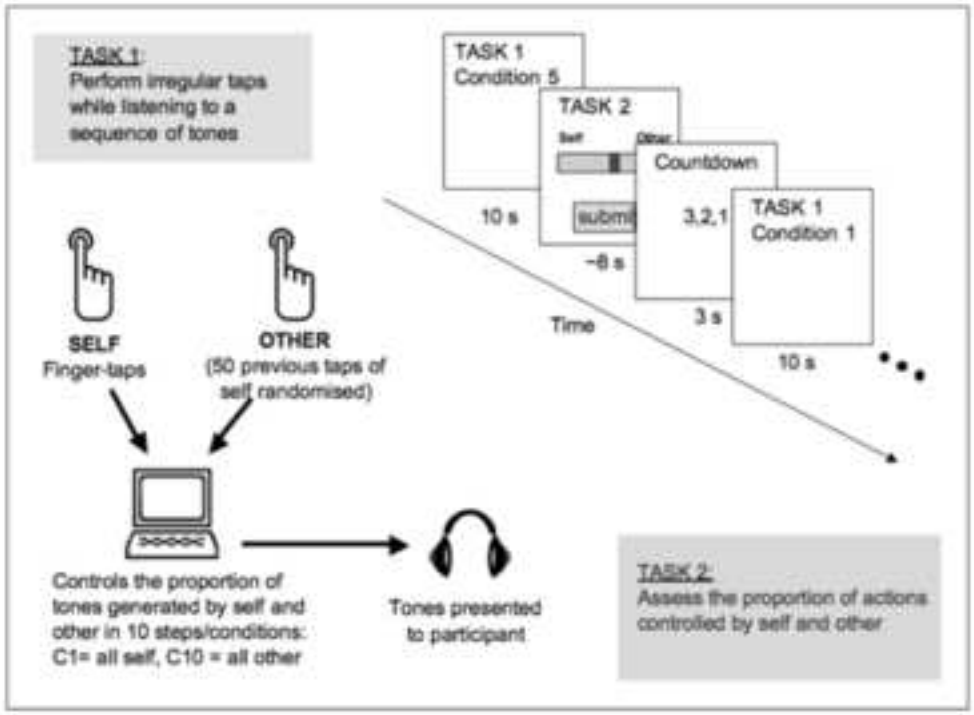

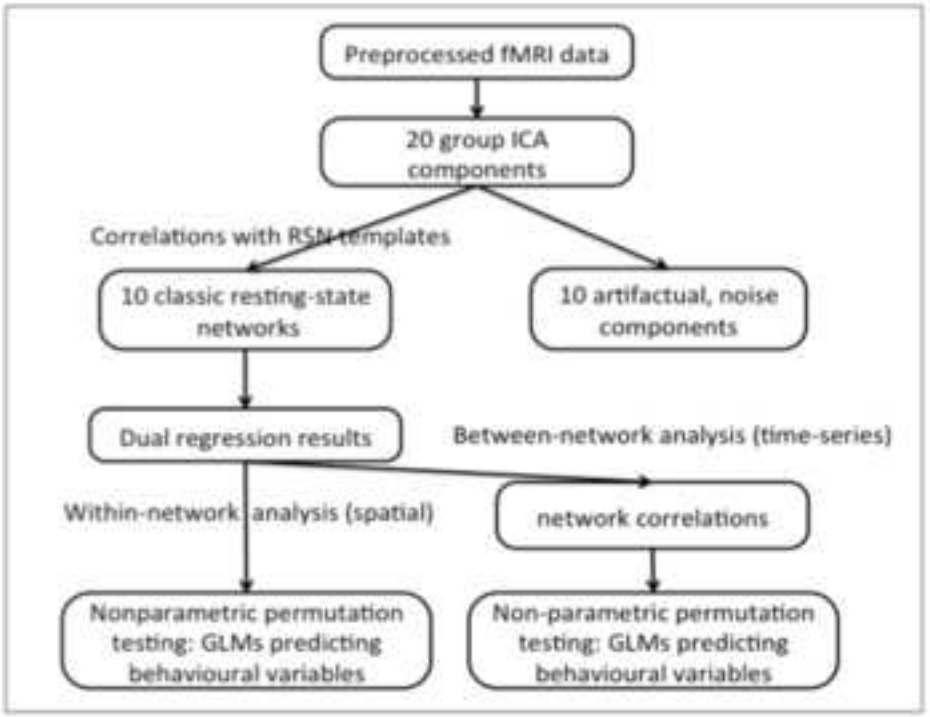

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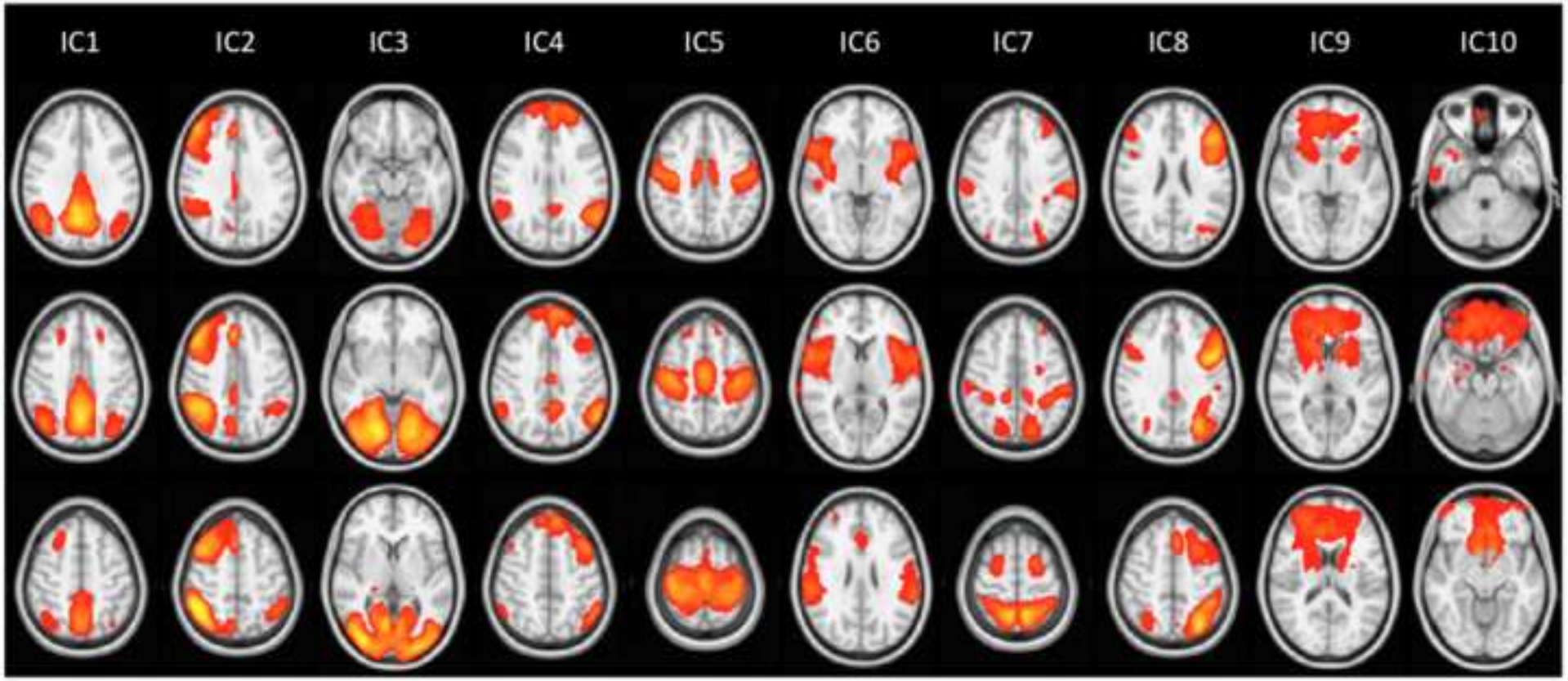

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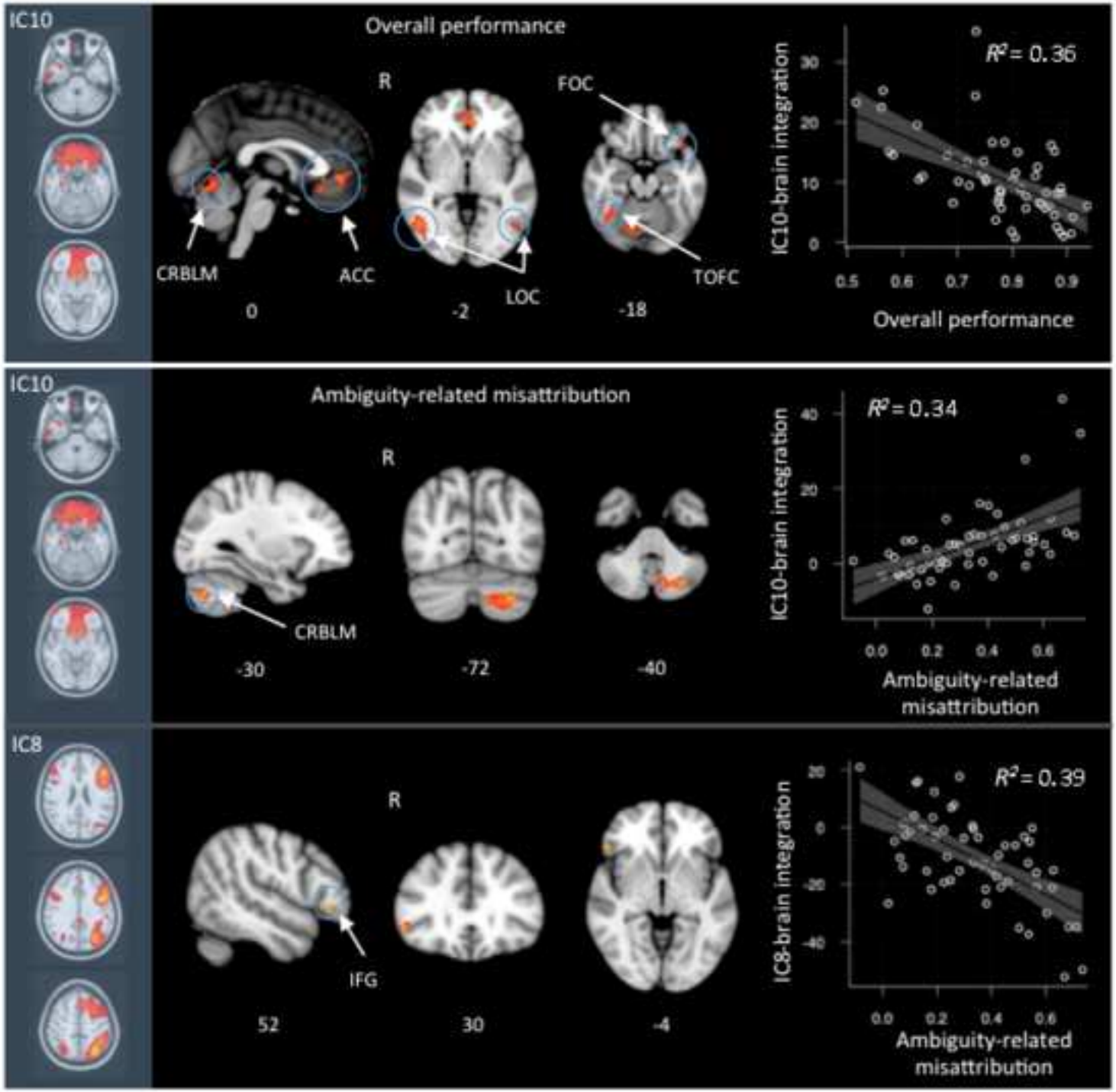

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